Alcohol Intake and Risk of Incident Melanoma

Table of Contents

Glossary of Abbreviations:

ALD2: Aldehyde dehydrogenase 2

BMI: Body Mass Index

CI: Confidence Interval

HPFS: Health Professionals' Follow-Up Study

LMM: Lentigo Maligna Melanoma

NHS: Nurses' Health Study

NHS II: Nurses' Health Study II

RR: Risk Ratio

SAS: Statistical Analysis System

SES: Socioeconomic Status

UVB: Ultraviolet B

UVR: Ultraviolet Radiation

Introduction

Cutaneous melanoma currently represents 5% of all new cancer diagnoses in the United States.[1] Even more alarmingly, the age-adjusted incidence of melanoma in the United States has climbed at an average estimated rate of 3% per year between 1975 and 2009, a period in which the incidence of most other malignancies has fallen.[2,3] Over a similar timeframe, spanning 1965 and 2002, beverage consumption in the United States increased from 11.8% to 21.0% of all calories consumed, and alcohol accounted for 32% of that increase. This amounts to an additional 71 kilocalories per person per day attributable to alcohol consumption.[4] As a result of the secular trend in melanoma incidence, approximately 1 in 50 Americans born in the year 2014 can expect to be diagnosed with invasive melanoma at some point during their lifetime, compared to 1 in 1500 for Americans born in 1935.[5] When cases of melanoma *in situ* are included, the lifetime risk of a melanoma diagnosis is even higher.[6]

Similar trends of escalating melanoma incidence have been documented worldwide and are particularly evident in countries with high levels of ultraviolet radiation (UVR) and majority light-skinned populations.[7-10] Some observers have questioned whether this represents a true increase in incidence, or merely an increased detection rate. For example, changes in medical practice related to the highly litigious medico-legal climate in the United States have been suggested as a driver of increased melanoma diagnoses.[11] However, while these factors may exert strong local effects, if the increase in melanoma diagnoses was solely or even primarily secondary to changes in medical practice or medico-legal climate, it would be unlikely to occur so uniformly across many different countries and legal systems.

Furthermore, studies of melanoma incidence in the United States have observed increased numbers of newly diagnosed melanomas across all tumor thicknesses and socioeconomic strata.[2] Tumor thickness is the most important factor in staging melanoma, and it is significant that more melanomas are being diagnosed all along the spectrum of tumor thickness. This argues against the claim that there has simply been increased detection of early and indolent melanomas. Similarly, the fact that all SES groups have seen increases in incident melanoma is significant in part because in the United States melanoma is more likely to be detected in higher SES groups, who may have better awareness of the disease as well as better access to the medical system.[12-13] Conversely, lower SES groups are more commonly diagnosed with melanoma in its advanced stages. The fact that both low and high SES groups have seen increased melanoma diagnoses, and that the increased diagnoses have spanned all tumor thicknesses, suggests that the observed trend toward higher melanoma incidence is

unlikely to be solely attributable to increased detection. Rather, it seems more likely that there are globally distributed behavioral or environmental changes that are causing increased exposure to modifiable risk factors, and thereby driving a real increased incidence of melanoma.

Well-established predictors of melanoma risk include a personal or family history of skin cancer, presence of atypical or numerous moles, high sun sensitivity (sunburning easily, difficulty tanning, natural red or blond hair color), immunosuppression, and intermittent ultraviolet radiation exposure. With the exception of UVR exposure, most of these predictors are non-modifiable host factors, which would be unlikely to cause such rapid changes in the incidence of melanoma. Modifiable lifestyle factors that have been linked to carcinogenesis in other cancers, such as alcohol and tobacco use, have been suggested in the literature but have never been definitively associated with melanoma.[14-18] Given the magnitude of the health concern, it is important to identify as many modifiable risk factors for melanoma as possible, both to delineate all contributors to the globally increasing incidence of melanoma and to aid in individual risk mitigation.

Consumption of alcoholic beverages is a major driver of neoplastic disease: based on the population attributable risk across all cancer types, approximately 3.6% of all cancers worldwide can be directly attributed to alcohol consumption.[19] The highest risk ratios from alcohol consumption have been documented for oropharyngeal and esophageal neoplasms, where the exposure to ethanol and its breakdown products are the highest. Other cancers for which there is a known association with alcohol consumption include the liver, colon, rectum, larynx and female breast.[19] As previously noted, the temporal correlation between the increase in daily calories from alcohol consumption in the United States and the increase in incident melanoma is also suggestive of the potential role that ethanol and its breakdown products might play, though this correlation provides no evidence of a causal relationship. In addition, it has been suggested that alcohol consumption might intensify sunburn severity and thereby increase risk of melanoma.[20] Given popular associations between alcohol consumption and outdoor activities like sunbathing, the suggested propensity of alcohol to exacerbate sunburns could also be a source of excess risk.[21]

Interest in the mechanisms of alcohol-mediated carcinogenicity has led to investigations finding that ethanol itself is not directly carcinogenic. Rather, ethanol is quickly metabolized into acetaldehyde, which is a Group I human carcinogen that readily forms Schiff-base adducts with DNA and cellular proteins.[22] These adducts are highly mutagenic and can also result in deleterious DNA-protein and DNA-DNA cross-links. This is a biologically plausible mechanism for carcinogenicity linked to alcohol consumption, and would be expected to contribute to

carcinogenicity in direct proportion to the concentration of acetaldehyde in the given tissue. Due to gender differences in the distribution and metabolism of ethanol, experimental evidence suggests that on average women will generate higher blood concentrations of acetaldehyde than men at the same levels of alcoholic beverage consumption.[23] As a result, one would hypothesize that on average women should exhibit higher risk ratios for acetaldehyde-mediated carcinogenesis than men at similar levels of alcohol consumption. This effect may be obscured in many studies, however, if men have a tendency to consume more alcohol than women even within a single consumption group (for example, if some research subjects are grouped together as "≤1 drink per day" for the purposes of analysis, men in that group may consume an average of 0.9 drinks per day while women in that group consume an average of 0.7 drinks per day).

In addition to the endogenous conversion of ethanol to acetaldehyde, alcoholic beverages also contain pre-existing acetaldehyde.[24] Producers of alcoholic beverages typically aim to keep acetaldehyde concentrations in their products low for better palatability, however higher levels of acetaldehyde may be present in alcoholic beverages that are produced using short fermentation times, or that are stored in the presence of oxygen prior to consumption. Typical levels of pre-existing acetaldehyde vary between beverage types, and have been shown to be high enough to case carcinogenesis.[24] For example, Calvados has been noted to have an higher pre-existing acetaldehyde content than most other alcoholic beverages and has been specifically associated with esophageal cancer independent of its ethanol content.[25-26] It is therefore possible that different types of alcoholic beverage may have varying risk profiles, with those beverages containing higher levels of pre-existing acetaldehyde conferring greater risk, even at similar levels of total ethanol consumption. So far, we know of no studies documenting differences in risk of incident melanoma between the major classes of alcoholic beverage (white wine, red wine, beer, liquor) after adjusting for their ethanol content.

There is evidence that consumption of alcohol and smoking exert synergistic effects in promoting the development of esophageal cancer.[27] There is no existing evidence to determine whether this or other forms of effect modification might also work to promote the development of melanoma. In addition to smoking status, it is possible that the effects of alcohol ingestion might be dependent on factors such as age or body mass index (BMI). For example, based on volume of distribution and tissue composition, one might hypothesize that individuals with lower BMI would be at increased risk of melanoma at similar levels of alcohol ingestion compared to individuals of higher BMI. We know of no previous studies investigating these possibilities.

With regard to existing evidence supporting an association between alcohol and melanoma, experimental studies in animals suggest that the clinical course of melanoma may

be more aggressive in the presence of ethanol.[28-29] This has never been demonstrated in humans however, and existing epidemiological evidence for an association between alcohol consumption and incidence of melanoma has been equivocal. Several case-control studies found positive associations between total alcohol intake and melanoma at moderate levels of consumption,[3, 30-32] while others found either trends toward increased risk that were not statistically significant[33-36] or no evidence of any association.[37-39] In one case-control study, a *decreased* risk of malignant melanoma was observed among a group of female alcoholics.[40] These inconsistencies may be due to a failure to adjust for relevant confounders in some of the studies cited, or due to other biases that can be particularly difficult to account for in the case-control method.

To date, there have been few cohort studies with data on alcohol and melanoma. Of those available, one cohort had too few cases of melanoma (n=6) from which to draw conclusions.[41] Another was limited to drinkers versus non-drinkers of beer and drinkers versus non-drinkers of wine/liquor, with no quantitative data available on the amounts of alcohol consumed.[42] Therefore, higher quality and more comprehensive evidence is warranted to evaluate the association between alcohol and melanoma.

The most comprehensive epidemiological study of this question is a recent meta-analysis by Rota et al, which included a total of sixteen studies (fourteen case-control and two cohort-based) totaling 6,251 cases of melanoma.[43] The authors used a non-linear meta-regression random effects model and found that when compared to no alcohol consumption or occasional alcohol consumption, regular alcohol consumption was associated with a pooled risk ratio of 1.20 (95% CI: 1.06-1.37) across all sixteen studies. When 'light' and 'moderate-to-heavy' drinkers were analyzed separately, the pooled risk ratio for 'light' alcohol consumption (≤1 drink per day) was 1.10 (95% CI 0.96-1.26), while the risk ratio for 'moderate-to-heavy' alcohol consumption (≥1 drink per day) was 1.18 (95% CI 1.01-1.40). This suggests a dose-response relationship between alcohol consumption and melanoma. Although results from the ≤1 drink per day consumption category did not reach statistical significance, it is unclear from these data whether a study powered to detect smaller differences in melanoma risk might also reveal a statistically significant increase in risk at those levels of alcohol consumption.

More concerning with regard to the scientific validity of the Rota et al analysis, there was no attempt to adjust for confounding by UVR exposure in six of the included sixteen studies. Among the ten studies for which there was at least some attempt at adjustment for UVR exposure, the pooled risk ratio was 1.15 (95% CI 0.94-1.41). In comparison, among the six studies for which there was no adjustment for UVR exposure the pooled RR was 1.27 (95% CI

1.20-1.25). Thus, the most strongly positive results come from studies in which there were no attempts to adjust for UVR, and when the unadjusted studies are excluded the pooled risk ratio is not statistically significant. This is highly concerning for residual confounding by UVR exposure, and suggests that the pooled risk ratios among all sixteen studies may overstate the magnitude of the association.

In our study, we investigated the association between alcohol and melanoma prospectively using a total population of 223,166 participants in the Nurses' Health Study (NHS), Nurses' Health Study II (NHS II), and Health Professionals' Follow-Up Study (HPFS). We assessed both total and type-specific alcohol consumption (beer, red wine, white wine, liquor) for an association with melanoma. We present findings from individual cohort analyses as well as from pooled analyses that were performed using a meta-analytic approach. We conducted additional analyses stratified by smoking status, caffeine intake, body mass index (BMI), and age in order to evaluate those factors as potential effect modifiers of the association between alcohol and melanoma. Since this is by far the largest cohort study of this question, we will be able to detect smaller differences in relative risk than were previously possible. Furthermore, we have taken great care to adjust for confounding by both host factors (age, body mass index, smoking status, sun sensitivity, number of nevi, hair color, and family history) and environmental factors (average UVB flux at place of residence, number of severe sunburns). This will ensure a higher degree of validity than is possible in the majority of the previously available studies.

Methods

Study Population

A total of 223,166 participants were followed for a mean of 19.0 years (4,236,166 person-years of data). Details on study population for each cohort study are presented in Supplementary Table S1. Briefly, the Nurses' Health Study (NHS) was established in 1976 when 121,700 married, female registered nurses aged 30–55 years in the United States returned a baseline questionnaire about their medical history and lifestyle. The Nurses' Health Study II (NHS II) comprises a cohort of 116,671 female nurses aged 25–42 years who returned a similar baseline questionnaire in 1989. The Health Professionals' Follow-Up Study (HPFS) began in 1986 when 51,529 men in health professions completed their baseline questionnaire. Participants in each cohort receive biennial follow-up questionnaires, and the response rate in each follow-up cycle typically exceeds 90**%**. Return of biennial questionnaire was considered as

informed consent in the studies. This study was approved by the Human Research Committee at the Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA, USA).

Assessment of Primary Exposure (Alcohol Intake)

Information on alcohol intake was collected every four years via a semi-quantitative food frequency questionnaire. These questionnaires were administered from 1980-2008 in the NHS, from 1991-2007 in the NHS II, and from 1986-2008 in the HPFS. Participants responded to the following question: "For each food listed, how often on average have you used the amount specified during the past year?" Five of the questions assessed the average intake of alcoholic beverages (non-light beer, light beer, red wine, white wine, and liquor) during the past year. Intake of each beverage was ascertained in nine categories (number of drinks): none or less than one per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, and 6+ per day. Responses for each category were coded as 0 drinks per week, 0.5 drinks per week, 1 drink per week, 3 drinks per week, 5.5 drinks per week, 7 drinks per week, 17.5 drinks per week, 31.5 drinks per week, and 49 drinks per week, respectively. The amount of alcohol in each beverage was estimated at 12.8 g for a glass, bottle, or can of either light or non-light beer (12 fl oz [355 mL]), 11 g for a glass of wine (4 fl oz [120 mL]), and 14 g for a shot of liquor (1.5 fl oz [45 mL]). Total alcohol intake (in grams) was computed as the sum of the intake from beer, wine, and liquor. Due to the paucity of participants in the higher intake categories, several of the highest consumption categories were combined in the final analysis. Cumulative alcohol intake was updated after each food frequency questionnaire in the Cox proportional hazards model. When reporting risk ratios per drink in the total alcohol intake analyses, one standard drink was defined as 12.8 g of alcohol (median amount of alcohol in one drink of beer, wine, or liquor). Beverage-specific consumption was calculated in units of "drinks per week" (as coded from the questionnaire responses) and analyzed separately. The reproducibility and validity of this questionnaire for alcohol intake have been previously documented in the NHS cohort.[44]

Assessment of Covariates (Biometric Data and Melanoma Risk Factors)

Covariates included age, body mass index, smoking status, sun sensitivity, average UVB flux at place of residence, number of severe sunburns, number of nevi, hair color, and family history. Beverage-specific analyses were additionally adjusted for total alcohol intake. Date of birth and height were reported on the baseline questionnaire in each cohort. Participants reported their current weight, smoking history, physical activity, caffeine intake, family history of

melanoma, tanning ability, lifetime number of severe sunburns, number of moles on forearms, hair color at age 18, and place of residence on the biennial mailed questionnaires. Quintiles of metabolic equivalents were calculated from questions about various types of physical activity. Body mass index was calculated as weight in kilograms divided by height in meters squared. Previously, the accuracy of self-reported anthropometric measures was validated among 140 NHS participants. Self-reported and measured weights were highly correlated (Pearson $r = 0.97$).[45] Average annual UV-B flux, a composite measure of mean UV-B radiation level based on latitude, altitude, and cloud cover, was estimated for all participants according to state of residence during follow-up.

Assessment of Outcomes (Invasive Melanoma and Melanoma in situ)

The outcomes of interest were incident invasive melanoma and incident melanoma *in situ*. Cases were ascertained from participants' responses to a question on physician-diagnosed melanoma on the biennial questionnaires. With their permission, the medical records of participants' who self-reported a diagnosis of melanoma were reviewed by physicians to confirm the diagnosis. Only incident cases of melanoma that were confirmed via pathology record review were included in the analysis. Cases of ocular or mucosal melanoma were excluded.

Statistical Analyses

Participants in the NHS, NHS II, and HPFS cohorts were excluded at baseline if they reported a personal history of cancer, a personal history of non-melanoma skin cancer, or non-white race/ethnicity. Those with a personal history of cancer, including non-melanoma skin cancer, were excluded due to concerns that such participants would likely have closer physician follow-up and therefore higher rates of melanoma detection than other participants on that basis alone. Participants of non-white race/ethnicity were excluded because of a lack of sufficient numbers of non-white participants in the NHS, NHS II, and HPFS cohorts from which to draw statistically valid conclusions. After application of exclusion criteria, 86,635 participants were included for analysis in the NHS cohort, 88,363 in the NHS II cohort, and 48,168 in the HPFS cohort. Person-years of follow-up for each participant were calculated from the return date of the baseline questionnaire (1980 for NHS, 1991 for NHS II, and 1986 for HPFS) to the date of diagnosis of melanoma, death, or the end of follow-up (June 2008 for NHS, June 2007 for NHS II, and January 2006 for HPFS), whichever came first. We used a Cox proportional hazards model updated by calendar time at 2-year intervals to estimate the age-adjusted and multivariate-adjusted risk ratio (RR) and 95% confidence interval (CI) for the association

between alcohol intake and incident melanoma. The covariates in the multivariate analysis were updated during follow-up, including age, BMI, smoking history, physical activity, caffeine intake, family history of melanoma, tanning ability, lifetime number of severe sunburns, number of moles on forearms, hair color at age 18, and average annual UV-B flux, if available. Separate beverage-specific analyses were additionally adjusted for total alcohol intake. Categories of exposure for the beverage-specific analyses were beer (combination of light and non-light beer from survey data), red wine, white wine, and liquor. The outcomes for the beverage-specific analyses were the same as the general analyses (invasive melanoma and melanoma *in situ*). We also performed statistical analyses after stratifying research subjects by age, smoking history, caffeine intake, physical activity, hair color, and BMI to assess for interactions. Finally, we performed a sensitivity analysis by excluding cases of lentigo maligna melanoma, a melanoma subtype that is highly UVR-dependent compared to other melanoma subtypes.

Next, we used a meta-analytic approach to evaluate pooled risk ratios for invasive and *in situ* melanoma as a function of alcohol intake. For these analyses we used data from all three cohorts to obtain an overall RR for all participants. We also performed a separate pooled analysis using data from only the NHS and NHS II cohorts to derive a pooled RR for women alone. We tested the heterogeneity between studies and estimated the overall association from random effects models (weighted proportionately to the inverse of the sum of the study-specific variance plus the common variance between studies) or fixed effects models (weighted proportionately to the inverse of the study-specific variance). All statistical analyses were conducted using the Statistical Analysis System software (SAS, version 9.1; SAS Institute, Cary, NC). All statistical tests were two tailed, and the significance level was set at $p < 0.05$.

Results

After application of exclusion criteria, we identified 612 cases of incident invasive melanoma and 359 cases of incident melanoma *in situ* among 86,635 women in the NHS cohort (1980-2008), 391 cases of incident invasive melanoma and 289 cases of incident melanoma *in situ* among 88,363 women in the NHS II cohort (1991-2007), and 493 cases of incident invasive melanoma and 222 cases of incident melanoma *in situ* among 48,168 men in the HPFS cohort (1986-2006). Basic cohort information is aggregated in Supplementary Table S1. Mean follow-up time was 22.6 years in the NHS, 17.0 years in the NHSII, and 16.0 years in the HPFS. Men in the HPFS were older (mean age = 54.2 years) than women in the NHS (mean age = 46.2 years) or NHS II (mean age = 36.1 years). Drinking patterns are presented in Supplementary

Table S2. Women in the NHS II drank the least (81% of participants drank less than 5g per day), followed by women in the NHS (65% drank less than 5g per day), while men in the HPFS drank the most (47% drank less than 5g per day). The women of the NHS II drank mostly light beer followed by white wine, while women in the NHS cohort drank mostly liquor followed by white wine. Among men, the highest alcohol intake was from liquor followed by non-light beer. In all other statistical analyses in this study, survey data reporting light and non-light beer are combined into a single 'beer' category.

Characteristics of the study population by drinking category are given in Table 1. Alcohol intake was positively associated with higher levels of smoking and caffeine consumption across all three cohorts. This pattern is consistent with known behavioral patterns relating the consumption of alcohol, tobacco, and caffeine, and was expected.[46] Alcohol intake was also positively associated with modestly increasing levels of physical activity as well as an increased proportion of participants with red or blond hair. Finally, in the NHS and NHS II cohorts, increasing alcohol consumption was positively associated with a modestly higher proportion of participants reporting 6+ lifetime severe sunburns. Other factors, including age, BMI, proportion of participants with 6+ moles ≥3mm on the left forearm, family history of melanoma, high skin sensitivity to sun, and UVB flux at place of residence, showed no correlation with alcohol consumption in any cohort.

Several characteristics varied between cohorts. Women in the NHS cohort reported higher levels of caffeine intake, lower levels of physical activity, and higher levels of current smoking than participants in the other two cohorts. Women in the NHS II cohort were more likely to have had a family history of melanoma and were more likely to have natural red or blond hair. As expected from the youngest cohort, women in the NHS II also had less extensive smoking histories than participants in the other two cohorts. Conversely, the HPFS cohort had a higher proportion of participants that had experienced 6+ sunburns that blistered in their lifetime, which may be related to the higher average age of that cohort.

Table 2 shows age- and multivariate-adjusted risk ratios (RRs) for the association between total alcohol intake and incidence of invasive melanoma. Alcohol intake was positively associated with invasive melanoma in the NHS II cohort (p trend = 0.01) and in the pooled analysis of all three cohorts (RR 1.14 per drink per day, 95% CI: 1.02-1.27, p trend = 0.02) after adjusting for covariates. When analyzed independently, the NHS and HPFS cohorts each showed trends toward elevated risk of invasive melanoma associated with alcohol use, but these trends did not reach statistical significance. The pooled analysis of the two women's cohorts did not reach statistical significance after adjusting for all covariates (p trend=0.10, data

not shown). The highest alcohol consumption category for the purposes of this analysis was ≥20g of ethanol ingested per day, which is roughly the equivalent of ≥1.5 drinks per day. At this rate of alcohol consumption, multivariate-adjusted risk ratios for invasive melanoma reached 1.21 in the NHS, 1.76 in the NHS II, and1.09 in the HPFS compared to the reference group of non-drinkers. In the pooled analysis, the risk ratio for the highest consumption group was 1.27 (95% CI: 1.03-1.55).

Data on the association between alcohol intake and melanoma *in situ* is presented in Supplementary Table S3. We found an elevated risk of incident melanoma *in situ* associated with alcohol consumption in the NHS cohort (p trend <0.01), in the NHS II cohort (p trend <0.01), and in the pooled analysis of both women's cohorts (RR 1.40 per drink per day, 95% CI: 1.19-1.64, p trend <0.01, data not shown). There was no association between alcohol intake and risk of incident melanoma *in situ* in the men's cohort (HPFS). In the pooled analysis of all three cohorts, total alcohol intake was positively associated with risk of incident melanoma *in situ* (RR 1.40 per drink per day, 95% CI: 1.19-1.64, p trend <0.01) after adjusting for all confounders. For melanoma *in situ*, the multivariate-adjusted risk ratios among the highest consumption group were 1.45 in the NHS, 1.46 in the NHS II, 0.90 in the HPFS, and 1.45 (95% CI: 1.04-2.03) in the pooled analysis.

Table 3 shows multivariate-adjusted and total alcohol intake-adjusted beverage-specific risk ratios for the association between beer (combined non-light and light beer from survey data), red wine, white wine, and liquor with risk of incident invasive melanoma. Consumption of white wine was associated with mild elevations in risk of invasive melanoma in the NHS cohort (RR 1.14 per drink per day, 95% CI: 1.00-1.31, p trend = 0.05), in the HPFS cohort (RR 1.19 per drink per day, 95% CI: 1.03-1.37, p trend = 0.02), and in the pooled analysis of all three cohorts (RR 1.14, 95% CI: 1.05-1.25, p trend <0.01). There was no association between white wine consumption and invasive melanoma In the NHS II cohort. There were no associations between beer, red wine, or liquor and incidence of invasive melanoma in any cohort.

Supplementary Table S4 shows the same beverage-specific analysis with incidence of melanoma *in situ* as the outcome of interest. Again, consumption of white wine was associated with an elevated risk of melanoma *in situ* in the NHS (RR 1.23 per drink per day, 95% CI: 1.06-1.42, p trend <0.01), NHS II (RR 1.23, 95% CI: 1.02-1.49, p trend = 0.03), and in the pooled analysis of all three cohorts (RR 1.17, 95% CI: 1.03-1.33, p trend = 0.02). There was no association between white wine consumption and incidence of melanoma *in situ* when the HPFS cohort was analyzed alone. No associations were found between beer, red wine, or liquor

and incidence of melanoma *in situ* in any cohort. These results for melanoma *in situ* are consistent with those for invasive melanoma.

Although all multivariate-adjusted analyses included several measures of UVR exposure, an additional sensitivity analysis was performed to assess for the potential of residual confounding by UVR exposure. To do so, a subtype of melanoma that occurs essentially exclusively on sun-damaged skin,[47] known as lentigo maligna melanoma (LMM), was excluded from the sensitivity analysis. If there were residual confounding by UVR exposure, we would expect the risk ratios to decrease when lentigo maligna melanomas were excluded from analysis, since they are a more UVR-dependent melanoma subtype and their numbers would therefore be most exaggerated by residual confounding by UVR exposure. The risk ratios for each beverage-type did not change materially when LMM cases were excluded from the analysis (data not shown), suggesting little risk of residual confounding by UVR exposure.

As noted previously, effect modification has been noted in the literature for the interaction between alcohol consumption and smoking as they pertain to the risk of certain esophageal carcinomas.[27] In that case, alcohol and smoking exerted a synergistic effect on risk of esophageal carcinoma. To investigate whether similar interactions might occur between alcohol consumption and relevant co-variables, we stratified our cohorts by age, BMI, smoking history, physical activity, natural hair color, and caffeine intake. Stratification along these variables revealed that the risk of melanoma associated with alcohol intake was not significantly modified by any of these factors, and none of the interaction terms were statistically significant (data not shown).

Discussion

In a pooled analysis of three large, prospective cohorts, we found that even moderate levels of alcohol consumption are associated with a modest but statistically significant increase in risk of both invasive melanoma (RR = 1.14 per drink per day) and melanoma *in situ* (RR = 1.40 per drink per day). These results support our initial hypothesis, and are consistent with the known association between alcohol consumption and other malignancies, as well as the proven carcinogenicity of the ethanol metabolite acetaldehyde. The clinical significance of these findings remains unclear, however, given the modest magnitude of the association. For comparison, the adjusted risk ratio of death from lung cancer among current smokers versus never smokers has recently been estimated at 14.6 for men and 17.8 for women, with other studies putting the risk ratio at 20 or more.[48,49] Clearly, the association between smoking and

lung cancer is highly clinically significant and a major public health concern, and has accordingly prompted major changes in public behavior regarding smoking. By comparison, the association that we have found between alcohol and melanoma may be of sufficient magnitude to drive new behaviors only in selected patient populations. In particular, for motivated patients with other strong risk factors for melanoma, counseling regarding alcohol use may be appropriate to reduce their risk. Patients particularly likely to benefit may be those with a personal or family history of melanoma. For most others, this evidence regarding the increased risk of melanoma with alcohol consumption is simply an additional reason to drink moderately (if at all), and comes as an additional health warning on top of the many other known deleterious effects of alcohol consumption on the body.

In addition to our main results in the pooled analysis, both Table 2 and Supplementary table S3 show evidence of a differential effect of alcohol consumption on men compared to women. Specifically, when stratified by gender, the association between alcohol consumption and melanoma was stronger in the two women's cohorts and weaker in the men's cohort. This is suggestive of effect modification by gender, which can be explained by known differences in the volume of distribution and metabolism of alcohol between men and women. As discussed in the introduction to this study, men on average have a greater volume of distribution of alcohol, greater gastric metabolism of alcohol, and consequently a lower blood alcohol content than women after imbibing equivalent doses of alcohol.[50,51] It is for these reasons that most national guidelines suggest lower maximum limits of alcohol consumption for women than for men.

In our analysis, we report risk ratios for men and women at equivalent levels of alcohol consumption. We again note that the effective dose of alcohol and acetaldehyde reaching the melanocytes will be higher in women (on average) than in men at the same level of alcohol consumption. Since it is the effective dose of alcohol and acetaldehyde reaching melanocytes that will affect the probability of developing melanoma, it is to be expected that the risk ratio of melanoma per alcoholic drink per day should be higher in the women's cohorts than in the men's, and that is what our results show. Indeed, the level of alcohol consumption reported by male participants in our study does not appear to have been high enough to significantly affect their melanoma incidence (the 95% confidence intervals cross 1.0 even for the highest consumption categories in the HPFS), despite being associated with a statistically significant increase in melanoma incidence in women. Based on our understanding of the mechanism of alcohol-associated carcinogenicity, we would expect that statistically significant increases in melanoma risk could be seen in men drinking higher amounts of alcohol than the men in our study reported. Further research will be required to prove this hypothesis.

In addition to gender, there are a few other variables that have also been known to affect the impact of alcohol consumption on carcinogenesis. As discussed previously, smoking status is a particularly good example of a variable that has been shown to have a synergistic effect with alcohol on risk of esophageal carcinoma.[27] Variables that we hypothesized might modify the effect of alcohol consumption on risk of melanoma were age, smoking history, caffeine intake, physical activity, hair color, and BMI. Age was chosen based on the idea that older persons may have less capacity both for metabolizing alcohol and for repairing cellular damage,[52] and therefore their risk of melanoma may be more affected by alcohol consumption than other participants. Smoking history was chosen based on data from other authors suggesting a synergistic effect between smoking and alcohol on carcinogenesis in other cancers.[27] Caffeine intake was chosen due to its positive correlation with alcohol consumption and because of the ability of caffeine to alter cellular metabolism in a manner that may inhibit cutaneous carcinogenesis.[53,54] Physical activity was chosen because of the cellular changes that occur with regular exercise, which might affect how alcohol is metabolized as well as the extent to which alcohol ingestion causes cellular damage.[54,55] Hair color was chosen as a proxy for host sensitivity to UVR, on the premise that the melanocytes of more UVR-sensitive hosts may be especially likely to be affected by alcohol consumption due to the higher levels of cellular damage to their melanocytes independently of alcohol consumption. Finally, BMI was chosen based on the hypothesis that individuals of lower BMI would be more at risk of alcohol-induced cellular damage given their lower volume of distribution of alcohol and therefore higher blood alcohol content at equivalent levels of consumption.

In order to test for effect modification, we stratified study participants along each of these variables independently and derived an interaction term for each (results not shown). None of the interaction terms were statistically significant, suggesting no effect modification by any of these variables. It remains possible that in future studies utilizing larger data sets and/or higher levels of alcohol consumption (and therefore presumably generating higher risk ratios), that one or more of these variables may have a significant interaction.

In addition to our overall assessment of the association between alcohol ingestion and melanoma, we also investigated the differential effect of consuming various types of alcohol on risk of melanoma. Other authors have noted that particular beverages, including Calvados, seem to have a particularly strong magnitude of effect on carcinogenesis that is over and above that which would be explained by its alcohol content alone.[25-26] This effect may be attributable to higher levels of pre-existing acetaldehyde in Calvados compared to other beverages, which would add to the effect of endogenously generated acetaldehyde. The amount of pre-existing

acetaldehyde typically found in alcoholic beverages is thought to be above levels considered carcinogenic,[24,56] and therefore may also be a significant contributor to the effects of alcohol consumption on melanoma. Although we did not have data on the consumption of specific beverages, we were able to perform analyses based on broad beverage categories (white wine, red wine, beer, and liquor).

We wanted to isolate the effect of pre-existing acetaldehyde in particular beverage types over and above the effect of the ethanol contained in those beverages. All of the analyses by beverage type are therefore adjusted for ethanol content, and the risk ratios reported in the beverage-specific analyses represent the effects of consuming beverages in those categories independently of their ethanol content. For example, when looking at invasive melanoma, a risk ratio of 1.3 per drink per day in the beverage-specific analysis would represent a risk ratio of 1.3 per drink per day for consuming a beverage in that class, in addition to the general risk ratio of 1.14 per drink per day for invasive melanoma when consuming any alcoholic beverage. The overall risk ratio for invasive melanoma when consuming that particular beverage would thus be higher than either its beverage-specific RR (1.3) or the general RR (1.14).

Previous research on the acetaldehyde content of various beverages has estimated the acetaldehyde content of various beverage classes as follows: spirits at 2,038 ± 3,101 µg/standard drink (range 0 - 34,769), beer at 2,257 ± 1,653 µg/standard drink (range 0 – 15,824), wine at 4,092 ± 4,023 µg/standard drink (range 0 – 25,298), and fortified wine at 10,671 ± 10,821 µg/standard drink (range 1,065 – 71,994).[24,56] The authors of that study also performed a subgroup analysis separating red and white wine, and found no significant difference in the acetaldehyde content between those two groups of wine. We would therefore anticipate that wine and fortified wine might be independently associated with higher risk of carcinogenesis compared to beer or liquor. We note that we cannot separate fortified from unfortified wines in our data, however we believe it is likely that the vast majority of reported white wine consumption is of the unfortified type.

In our beverage-specific analysis we found that consumption of white wine was the only beverage type associated with statistically significant increases in risk of both invasive and *in situ* melanoma beyond that attributable to ethanol content. Specifically, in the pooled analysis of all three cohorts, consumption of white wine was associated with a relative risk of invasive melanoma of 1.14 per drink per day on top of the general risk from the ethanol contained in the wine. Consumption of white wine was also associated with increased risk of invasive melanoma in the NHS (RR = 1.14 per drink per day) and HPFS (RR 1.19 per drink per day), but did not reach statistical significance for the continuous variable in the NHS II. Similarly, we found an

association between the consumption of white wine and increased risk of incident melanoma *in situ* in the pooled analysis (RR 1.17 per drink per day), as well as in the NHS (RR 1.23 per drink per day) and NHS II (RR 1.23 per drink per day), but not in the HPFS. None of the other beverage categories that we analyzed (red wine, beer, liquor) showed any association with either invasive melanoma or melanoma *in situ* in any cohort or pooled analysis.

If the association between white wine and incident melanoma is real, as opposed to a chance finding, we believe that the much higher pre-existing acetaldehyde content of wine versus beer or liquor is the most likely explanatory factor driving that association. If that is the case, we presume that the pre-existing acetaldehyde content of beer and liquor was not sufficient to cause a large enough effect to be detected in our study. Since there has not been an association specifically between white wine and carcinogenesis before, this finding will need to be replicated in further studies to ensure that it is robust. With that said, the acetaldehyde content of each beverage type alone does not explain the differences we observed between red wine and white wine consumption. As mentioned, investigators who have studied the acetaldehyde content of wine previously found no difference between the acetaldehyde content of red versus white wines.[24,56]

One possible explanation for our results is that the higher phenolic content in red wines compared to other alcoholic beverages confers a protective benefit on red wine drinkers. Phenols are known to have antioxidant effects, which could counteract or otherwise compensate for the carcinogenic effects of acetaldehyde exposure. We also considered the possibility of residual confounding by UVR exposure among white wine drinkers. For example, although we controlled for many factors influencing UVR exposure, white wine may be more associated with drinking outdoors in the summer months than other beverage types. One way that we attempted to minimize the chances of this kind of residual confounding by UVR was by sensitivity testing. It has been recently discovered that lentigo maligna melanoma (LMM) is significantly associated with UVR exposure in the NHS, NHSII, and HPFS cohorts, whereas other melanoma subtypes are not significantly associated with UVR exposure in these cohorts (unpublished data). By excluding LMM from the analysis, we reduce the UVR-dependence of our results. Therefore, if the association between white wine and melanoma that we found was caused by residual confounding by UVR exposure, it should disappear once LMM are excluded. The association between white wine and invasive melanoma in this study was not sensitive to the exclusion of LMM (data not shown), and it therefore seems unlikely that the association between white wine and melanoma is mediated by residual confounding from UVR exposure.

Finally, the differences in our beverage specific results for red and white wine are unlikely to be caused by the sample sizes used, which were similar between white wine, red wine, and liquor.

Limitations & Suggestions for Future Work

The generalizability of our study may be limited by the lack of diversity in our cohorts; all participants were white, educated Americans who worked in healthcare settings. This lack of diversity is advantageous in the sense that it makes residual confounding by socioeconomic status, race/ethnicity, healthcare access, or health literacy much less likely. On the other hand, however, there is reason to believe that the carcinogenicity of alcohol consumption may vary between populations, and detecting these differences will require further research with more diverse cohorts. For example, the frequency of important genetic polymorphisms in the aldehyde dehydrogenase 2 (ALDH2) gene varies between populations. Individuals with the heterozygous ALDH2*1/*2 genotype are not able to metabolize acetaldehyde as quickly as those with the homozygous ALDH2*1/*1 genotype (which encodes the more active isozyme). As a consequence, heterozygous individuals develop higher blood and saliva acetaldehyde levels and exhibit higher levels of acetaldehyde-related DNA adducts after consumption of alcohol.[57-60] In one study, heavy drinkers who were heterozygous for ALDH2 were up to 12 times more likely to develop esophageal cancer compared to heavy drinkers who were homozygous for the active enzyme.[61-62] We expect that this relationship between ALDH2 genotype and risk of neoplasia would hold true for melanoma as well, however we did not have access to our participants genetic information to assess for such an effect.

Although this is the largest prospective study of alcohol consumption and melanoma, our analysis is limited by the relative paucity of participants reporting heavy drinking in these cohorts. We were therefore unable to investigate the risk of higher levels of alcohol intake. As a result of the gender differences in alcohol metabolism that were previously described, we are particularly concerned that the rates of alcohol consumption reported by men in this study may not have been sufficient to generate increases in melanoma risk of a magnitude to be statistically detectable in that group. Finally, because this is the first study that we are aware of to report an association specifically between white wine consumption and carcinogenesis, that finding will be subject to verification in separate cohorts to ensure its validity.

Conclusions

Our results are compatible with known associations between alcohol consumption and carcinogenesis in other cancer types, as well as with several previous case-control studies that

found associations between total alcohol intake and melanoma incidence. We suggest that all individuals limit themselves to no more than moderate alcohol consumption given the negative effects of alcohol consumption on many organ systems, including the skin. For individuals at particularly high risk of melanoma, it may be prudent to be even more conservative with regard to alcohol consumption as well as UVR exposure.

Acknowledgements & Statement of Individual Author Contributions

The idea to use the NHS, NHS II, and HPFS databases to study the association between alcohol and melanoma was proposed by Andrew Rivera, and discussed and approved by Abrar Qureshi. The design of the study was proposed by Andrew Rivera in conjunction with Abrar Qureshi and modified according to guidance from Jiali Han and Tricia Li. Andrew Rivera, Abrar Qureshi, Jiali Han, and Tricia Li each contributed to the interpretation of the data and suggestions for additional analyses. All statistical programming was performed by Tricia Li. Andrew Rivera wrote the manuscript, which was reviewed by Abrar Qureshi and later by Eunyoung Cho. All survey data was collected by staff at the Channing Laboratory, and reported cases of melanoma were verified against medical records by Hongmei Nan. None of the authors had any personal or financial conflicts of interest. We would like to thank the participants and staff of the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-Up Study for their valuable contributions.

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Table 1. Age-adjusted characteristics of study population according to average alcohol intake

Characteristics	Average alcohol intake, g per day				
	None	0.1-4.9	5.0-9.9	10.0-19.9	20.0+
NHS (women) n = 86,635 at baseline in 1980	**n = 27580**	**n = 29063**	**n = 9434**	**n = 13245**	**n = 7313**
Mean alcohol intake, g per day	0.0 (0.0)	1.9 (1.2)	7.0 (1.2)	13.4 (2.5)	35.1 (12.3)
Mean age, years	46.4 (7.3)	45.5 (7.3)	46.0 (7.2)	46.8 (7.0)	47.4 (6.8)
Mean BMI, kg m^{-2}	25.3 (5.1)	24.5 (4.4)	23.7 (3.8)	23.3 (3.6)	23.3 (3.5)
Physical Activity, metabolic equivalents per week	12.1 (18.3)	14.2 (20.7)	15.8 (21.1)	16.0 (22.5)	14.6 (19.0)
6+ sunburns that blistered in lifetime, %	6.2	7.2	8.7	8.8	9.7
6+ moles ≥3mm on left forearm, %	4.7	4.9	4.9	4.5	4.3
Natural red/blond hair color at age 18, %	15	15.5	16.2	16.8	17.2
Family history of melanoma*, %	2.9	2.7	2.8	2.8	2.7
High skin sensitivity to sun**, %	16.5	14.5	13.5	13.3	13.9
Current smoking, %	22.8	27.3	30.5	35.3	46.6
Past smoking, %	20.3	28.5	33.0	35.5	31.5
Mean pack-years among ever smokers	21.3 (17.0)	18.8 (15.5)	19.4 (15.8)	20.4 (16.4)	25.3 (18.6)
UVB flux at residence in 1986, RB counts x 10^{-4}	122 (25)	120 (23)	121 (24)	122 (25)	125 (26)
Caffeine, mg/d	357 (278)	397 (267)	417 (264)	421 (259)	432 (259)
NHS II (women) n = 88,363 at baseline in 1991	**n = 37134**	**n = 34593**	**n = 8789**	**n = 5854**	**n = 1993**
Mean alcohol intake, g per day	0.0 (0.0)	2.1 (1.2)	7.1 (1.4)	13.2 (2.4)	32.5 (12.4)
Mean age, years	36.2 (4.7)	35.9 (4.7)	35.9 (4.7)	36.5 (4.7)	37.4 (4.4)
Mean BMI, kg m^{-2}	25.5 (5.9)	24.3 (5.1)	23.3 (4.0)	23.3 (4.0)	23.5 (4.1)
Physical Activity, metabolic equivalents per week	18.4 (25.1)	21.6 (27.1)	24.0 (29.9)	25.0 (29.2)	25.0 (32.0)
5+ sunburns that blistered in lifetime, %	9.1	10.0	10.9	11.0	12.1
5+ moles ≥3mm on bilateral lower legs, %	21.5	22.1	22.5	22.4	21.3
Natural red/blond hair color at age 18, %	19.7	20.4	22.2	22.8	24.2
Family history of melanoma*, %	4.1	4.3	4.9	4.9	4.7
High skin sensitivity to sun**, %	26.3	23.5	22.0	20.3	22.2
Current smoking, %	9.4	12.6	15.1	20.0	31.4
Past smoking, %	16.5	24.4	31.0	32.8	33.6
Mean pack-years among ever smokers	12.9 (9.2)	11.4 (8.4)	10.9 (7.9)	11.6 (8.4)	13.1 (9.0)
UVB flux at residence, RB counts x 10^{-4}	125 (24)	123 (24)	125 (25)	127 (25)	130 (26)
Caffeine, mg/d	198 (209)	254 (215)	295 (213)	317 (214)	350 (225)
HPFS (men) n = 48,168 at baseline in 1986	**n = 11244**	**n = 11585**	**n = 6991**	**n = 9870**	**n = 8478**
Alcohol intake, g per day	0.0 (0.0)	2.5 (1.2)	7.3 (1.4)	14.2 (2.6)	39.1 (16.7)
Age, years	54.7 (10.0)	53.6 (10.0)	53.4 (9.8)	54.3 (9.6)	55.1 (9.6)
BMI, kg m^{-2}	25.7 (3.6)	25.6 (3.4)	25.4 (3.3)	25.4 (3.2)	25.5 (3.2)
Physical Activity, metabolic equivalents per week	18.4 (26.7)	20.1 (27.7)	22.3 (31.5)	22.8 (32.0)	22.0 (30.2)
6+ sunburns that blistered in lifetime	34.7	34.3	34.5	35.7	38.5
6+ moles ≥3mm on bilateral forearms, %	5.8	5.5	5.2	5.1	5.3
Natural red/blond hair color at age 18, %	13.6	12.8	13.4	14.4	15.6
Family history of melanoma*, %	2.9	3.2	2.8	3.1	3.2
High skin sensitivity to sun**, %	27.3	25.8	24.2	23.8	23.4
Current smoking, %	7.3	7.8	8.7	10.3	17.2
Past smoking, %	32.9	40.6	45.2	50.3	54.5
Mean pack-years among ever smokers	27.3 (20.8)	24.1 (18.7)	24.1 (19.0)	24.1 (18.0)	28.8 (20.5)
UVB flux at residence in 1988, RB counts x 10^{-4}	133 (28)	128 (27)	128 (27)	129 (28)	131 (28)
Caffeine, mg/d	190 (227)	210 (220)	226 (217)	244 (223)	290 (238)

◆ Values are reported as mean (standard deviation) or as percentages. All variables (except age) are standardized to the age-distribution of the study population.
*Defined as father, mother, sister, or brother previously diagnosed with melanoma.

Table 2. Age-adjusted and multivariate-adjusted risk ratios (RRs) and pooled estimates for incident invasive melanoma by amount of average alcohol intake

Alcohol intake, grams per day	Number of incident cases	Age-adjusted RR (95% CI)	Multivariate* RR (95% CI)
NHS (women)			
0	223	*Reference*	*Reference*
0.1-4.9	191	1.09 (0.90-1.33)	1.07 (0.88-1.31)
5-9.9	66	1.12 (0.85-1.48)	1.08 (0.81-1.43)
10-19.9	81	1.11 (0.86-1.44)	1.07 (0.82-1.40)
20+	51	1.27 (0.91-1.68)	1.21 (0.88-1.66)
Total	**612**	P (trend) = 0.18	P (trend) = 0.32
NHS II (women)			
0	126	*Reference*	*Reference*
0.1-4.9	156	1.37 (1.08-1.73)	1.42 (1.11-1.80)
5-9.9	44	1.22 (0.86-1.72)	1.26 (0.88-1.79)
10-19.9	45	1.52 (1.08-2.14)	1.57 (1.10-2.25)
20+	20	1.67 (1.04-2.69)	1.76 (1.08-2.87)
Total	**391**	P (trend) = 0.01	P (trend) = 0.01
HPFS (men)			
0	118	*Reference*	*Reference*
0.1-4.9	113	1.02 (0.79-1.32)	1.03 (0.80-1.34)
5-9.9	55	0.82 (0.60-1.14)	0.83 (0.60-1.15)
10-19.9	112	1.12 (0.86-1.45)	1.14 (0.86-1.46)
20+	95	1.13 (0.86-1.48)	1.09 (0.88-1.55)
Total	**493**	P (trend) = 0.24	P (trend) = 0.19
Meta-analysis (all cohorts)		**Age-adjusted RR (95% CI)**	**Multivariate* RR (95% CI)**
0	467	*Reference*	*Reference*
0.1-4.9	460	1.15 (0.98-1.36)	1.16 (0.96-1.40)
5-9.9	165	1.04 (0.83-1.30)	1.04 (0.83-1.30)
10-19.9	238	1.20 (1.00-1.44)	1.20 (0.97-1.48)
20+	166	1.24 (1.03-1.50)	1.27 (1.03-1.55)
Per drink/day† (continuous)	**1496**	1.14 (1.03-1.26) P (trend) = 0.01	1.14 (1.02-1.27) P (trend) = 0.02

*Multivariate estimates are adjusted for age, BMI, smoking status, physical activity, caffeine intake, family history of melanoma, tanning ability, lifetime number of severe sunburns, number of moles on forearms, hair color at age 18, and average annual UV-B flux at place of residence.
†Risk ratios per drink per day were estimated based on a standard drink containing 12.8 grams of alcohol.

Table 3. Multivariate alcohol-adjusted RRs for invasive melanoma according to beverage-specific alcohol intake

NHS (women)								
Drinks Consumed	**Beer**		**Red wine**		**White wine**		**Liquor**	
	Incident Cases	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**
None	496	Ref.	354	Ref.	291	Ref.	417	Ref.
1-3 per month	49	0.81 (0.60, 1.10)	94	1.38 (1.06, 1.79)	110	1.00 (0.77, 1.28)	73	0.86 (0.66, 1.12)
1 per week	23	1.00 (0.65, 1.54)	31	1.23 (0.81, 1.86)	46	1.04 (0.72, 1.48)	42	1.14 (0.82, 1.59)
2-4 per week	28	0.82 (0.55, 1.21)	44	1.97 (1.37, 2.83)	49	0.97 (0.68, 1.38)	79	0.92 (0.71, 1.19)
≥5 per week	16	0.93 (0.56, 1.54)	16	1.02 (0.61, 1.72)	43	1.35 (0.96, 1.91)		
Per drink/day† (continuous)	612	1.06 (0.87, 1.30) P (trend) =0.54	539	1.03 (0.85, 1.24) P (trend) = 0.78	539	1.14 (1.00, 1.31) P (trend) = 0.05	611	0.96 (0.83, 1.11) P (trend) = 0.60
NHS II (women)								
Drinks Consumed	**Beer**		**Red wine**		**White wine**		**Liquor**	
	Incident Cases	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**
None	249	Ref.	267	Ref.	198	Ref.	301	Ref.
1-3 per month	52	1.16 (0.85, 1.59)	51	0.75 (0.54, 1.03)	99	1.34 (1.03, 1.75)	58	0.96 (0.71, 1.28)
1 per week	16	0.95 (0.56, 1.59)	36	1.26 (0.85, 1.88)	41	1.35 (0.92, 1.99)	16	0.76 (0.45, 1.28)
2-4 per week	55	1.19 (0.87, 1.63)	51	0.82 (0.50, 1.33)	36	1.69 (1.13, 2.52)	14	0.74 (0.42, 1.27)
≥5 per week	17	1.39 (0.84, 2.31)	14	1.26 (0.72, 2.21)	15	1.23 (0.71, 2.13)		
Per drink/day† (continuous)	389	1.10 (0.68, 1.78) P (trend) =0.70	419	1.10 (0.88, 1.38) P (trend)= 0.42	389	1.06 (0.86, 1.30) P (trend) = 0.59	389	0.84 (0.61, 1.16) P (trend) = 0.29

Table 3 (Continued). Multivariate alcohol-adjusted RRs for invasive melanoma according to beverage-specific alcohol intake

HPFS (men)								
Drinks Consumed	**Beer**		**Red wine**		**White wine**		**Liquor**	
	Incident Cases	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**
None	216	Ref.	273	Ref.	220	Ref.	225	Ref.
1-3 per month	83	1.02 (0.78, 1.33)	75	0.66 (0.49, 0.88)	117	1.13 (0.87, 1.46)	92	1.58 (1.21, 2.05)
1 per week	38	0.89 (0.62, 1.28)	51	0.82 (0.58, 1.17)	68	1.24 (0.90, 1.72)	46	1.43 (1.02, 2.00)
2-4 per week	97	0.99 (0.75, 1.29)	53	0.92 (0.65, 1.30)	47	0.97 (0.68, 1.40)	129	1.22 (0.96, 1.55)
≥5 per week	56	1.05 (0.76, 1.43)	38	0.92 (0.64, 1.34)	40	1.66 (1.15, 2.39)		
Per drink/day† (continuous)	490	1.02 (0.89, 1.16) P (trend)= 0.81	490	1.03 (0.89, 1.19) P (trend)= 0.70	492	1.19 (1.03, 1.37) P (trend)= 0.02	492	1.02 (0.90, 1.16) P (trend)= 0.73
Meta-analysis (all cohorts combined)								
Drinks Consumed	**Beer**		**Red wine**		**White wine**		**Liquor**	
	Incident Cases	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**	**Incident Cases**	**Risk Ratio**
None	961		894	Ref.	709	Ref.	943	
1-3 per month	184	0.99 (0.81, 1.20)	220	0.88 (0.55, 1.42)	326	1.14 (0.96, 1.35)	223	1.09 (0.75, 1.59)
1 per week	77	0.94 (0.73, 1.20)	118	1.07 (0.80, 1.42)	155	1.20 (0.98, 1.47)	104	1.13 (0.82, 1.55)
2-4 per week	180	1.01 (0.83, 1.22)	148	1.15 (0.66, 2.00)	132	1.16 (0.82, 1.64)	222	1.00 (0.77, 1.29)
≥5 per week	89	1.08 (0.86, 1.37)	68	1.02 (0.78, 1.33)	98	1.44 (1.15, 1.81)		
Per drink/day† (continuous)	1491	1.03 (0.93, 1.15) P (trend)=0.54	1448	0.98 (0.84, 1.14) P (trend)= 0.76	1420	1.14 (1.05, 1.25) P (trend) < 0.01	1492	1.04 (0.91, 1.18) P (trend)=0.57

◆ Values are reported as multivariate alcohol-adjusted risk ratios (lower bound of 95% confidence interval, upper bound of 95% confidence interval). The covariates in this model are age, BMI, smoking status, physical activity, caffeine intake, family history of melanoma, tanning ability, lifetime number of severe sunburns, number of moles on forearms, hair color at age 18, and average annual UV-B flux at place of residence, and total alcohol intake.

‡The highest consumption category for liquor is “2+ drinks per week”.

†Risk ratios per drink per day were estimated based on a standard drink containing 12.8 g of alcohol.